Summary of the risk management plan for eptacog beta (activated) recombinant coagulation factor VII

This is a summary of the risk management plan (RMP) for Cevenfacta®. The RMP details important risks of Cevenfacta®, how these risks can be minimised, and how more information will be obtained about Cevenfacta®'s risks and uncertainties (missing information).

Cevenfacta®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cevenfacta® should be used.

This summary of the RMP of Cevenfacta® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cevenfacta®'s RMP.

I. The medicine and what it is used for

CEVENFACTA is authorised for adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:
• in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e., ≥5 Bethesda Units (BU);
• in patients with congenital haemophilia with low-titer inhibitors (BU <5) but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.

Further information about the evaluation of Cevenfacta®'s benefits can be found in Cevenfacta®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/cevenfacta

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Cevenfacta® together with measures to minimise such risks and the proposed studies for learning more about Cevenfacta® risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (*e.g.*, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Cevenfacta®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Cevenfacta® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Cevenfacta® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cevenfacta®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (*e.g.*, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Anaphylactic reactions Thromboembolic events Immunogenicity
Missing information	Patients with hepatic or renal impairment Elderly patients Pregnant and breastfeeding women

II.B Summary of important risks

Important identified risks
None

Important potential risks

Anaphylactic reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions and anaphylaxis have been observed in clinical trials and post-marketing setting

	with medicinal products of the same therapeutic class [*Novoseven EPAR*, *Novoseven EU PI*]. Important potential risk of anaphylactic reaction cannot be ruled out and must then be considered as a potential class effect
Risk factors and risk groups	Patients with known IgE-based hypersensitivity to rabbit proteins may be at higher risk of anaphylactic reactions.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.3 & 4.4 PL sections 2 & 4 <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries See section II.C of this summary for an overview of the post-authorisation development plan.

Thromboembolic events	
Evidence for linking the risk to the medicine	Venous and arterial thromboembolic events have been observed in clinical trials and post-marketing setting with medicinal products of the same therapeutic class [*Novoseven EPAR*, *Novoseven EU PI*]. Clinical experience with pharmacologic use of FVIIa-containing products indicates an elevated risk of serious thrombotic events when used simultaneously with activated prothrombin complex concentrates.
Risk factors and risk groups	Possible risk factors include: • History of atherosclerotic disease, coronary artery disease, cerebrovascular disease, crush injury, septicaemia, or thromboembolism. • History of congenital and acquired haemophilia receiving concomitant treatment with aPCC/PCC (activated or non-activated prothrombin complex) or other haemostatic agents
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4 PL sections 2 & 4 <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries

Immunogenicity	
Evidence for linking the risk to the medicine	In clinical trials of patients with factor VII deficiency, formation of antibodies against NovoSeven and FVII has been reported. Development of inhibitory antibodies to NovoSeven has been reported in a post-marketing observational registry of patients with congenital FVII deficiency [*Novoseven EU PI*]. In post-marketing experience, there have been no reports of inhibitory antibodies against NovoSeven or FVII in patients with haemophilia A or B [*Novoseven EU PI*].
Risk factors and risk groups	As no case of neutralizing antibodies was observed during clinical development with eptacog beta (activated), no risk factor could be suggested.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4 PL sections 2 & 4 <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries

<u>Missing information</u>

Patients with hepatic or renal impairment	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4 PL section 2 <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries

Elderly patients	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4 PL section 2 <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	Collaboration with EUHASS registry

Pregnant and breastfeeding women	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.6 PL section 2 <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	Collaboration with EUHASS registry

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of Cevenfacta®.

II.C.2 Other studies in post-authorisation development plan

Collaboration with EUHASS registry:

- Background: EUHASS is a pharmacovigilance program to monitor the safety of treatments for people with inherited bleeding disorders in Europe. This is a prospective adverse event reporting system for patients with haemophilia and inherited bleeding disorders. Haemophilia treatment centres report adverse events directly to the EUHASS website and regular surveillance reports are produced [*Makris 2*011].
- Objectives: to further characterize the safety profile in patients exposed to eptacog beta (activated) and to estimate the event rates of the following important risks (hypersensitivity reactions, thromboembolic events, immunogenicity, and drug-drug interactions with activated or non-activated prothrombin complex or other haemostatic agents) including patients with hepatic or renal impairment and elderly patients.

Collaboration with PedNet registry:

- Background: The PedNet Haemophilia Registry is a multicenter, observational birth cohort followed in one of the participating haemophilia treatment centres (HTC's) to investigate natural history, safety and efficacy of replacement and non-replacement therapies in children and adolescents (12 years of age and older) with haemophilia A and B. The PedNet Haemophilia registry study group is an established network in the 31 haemophilia treatment centres (HTCs) from 18 countries specialized in the treatment of children and adolescents (12 years of age and older) with haemophilia. The cohort population concerns children and adolescents (12 years of age and older) with mild (FVIII/IX 6 to 25%), moderate (FVIII/IX 1 to 5%) or severe (FVIII/IX<1%) haemophilia A and B born from January 1st, 2000, onwards followed in one of the participating centres. The PedNet Haemophilia Registry is owned and administered by the PedNet Haemophila Research Foundation. As of December 1st, 2016, the PedNet Registry is registryed on http://ClinicalTrials.gov (n° NCT02979119). The PedNet Registry is also registered in the European Union electronic Registry of Post-

Authorisation Studies (PAS) of the European Network of Centres for Pharmacovigilance (ENCePP).

- Objective: to generate information regarding the use and the safety of eptacog beta (activated) in patients from 12 years old (including those with hepatic or renal impairment) in the post-authorisation setting. The PedNet Haemophilia registry follows the guideline for FVIII/IX of the European Medicines Agency (EMA). At baseline several variables are collected including data on patient, date of diagnosis, co-morbidity, gene mutation, family history of haemophilia and inhibitors. For the first 75 exposure days, date, reason, dose, and product are recorded for each infusion. For inhibitor patients, results of all inhibitor- and recovery tests are collected. For continued treatment, data on bleeding, surgery, prophylaxis, and clotting factor consumption are collected annually. Detailed information on haemophilia treatment, suspected adverse drug reactions and long-term outcome are collected in the centers from diagnosis onward. Data entry continues throughout the year by data registrars in the participating centers using a web-based Case Report Form **(**CRF).